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(54) Title: USE OF STEROID COMPOUNDS TO PREVENT NON-CANCEROUS TISSUE GROWTH

(57) Abstract

Compounds for use in preventing non-cancerous tissue growth are disclosed. Pharmaceutical compositions of the compounds and methods for their use in preventing non-cancerous tissue growth are disclosed.

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IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

USE OF STEROID COMPOUNDS TO PREVENT NON-CANCEROUS TISSUE GROWTH

Priority is claimed from the provisional application, U.S. Patent Application Serial No. 60/019060, filed May 9, 1996.

Field of the Invention

This invention relates to compounds and their use in methods and compositions for preventing and treating diseases in mammals, particularly humans, in which non-cancerous tissue growth plays a pathogenic role.

Description of Related Art

Steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., *A New Class of Steroids Inhibits Angiogenesis In The Presence of Heparin or Heparin Fragment*, Science, 230, pp. 1375-1378 (December 20, 1985). The authors refer to such steroids as "angiostatic" steroids. Included in the new class of steroids found to be angiostatic are cortisol, cortexolone, and several dihydro and tetrahydro derivatives. In a follow up study directed to testing a hypothesis as to the mechanism by which the steroids inhibit angiogenesis, it was shown

that heparin/angiostatic steroid compositions caused dissolution of the basement membrane scaffolding to which anchorage dependent endothelia are attached resulting in capillary involution; see, Ingber, et al. *A Possible Mechanism for Inhibition of Angiogenesis by Angiostatic Steroids: Induction of Capillary Basement Membrane Dissolution*, Endocrinology 119, pp. 1768-1775 (1986).

A group of tetrahydro angiostatic steroids useful in inhibiting angiogenesis is disclosed in International Patent Application WO 87/02672 (Aristoff et al.). The compounds are disclosed for use in treating head trauma, spinal trauma, septic or traumatic shock, stroke, and hemorrhagic shock. In addition, the patent discusses the utility of these compounds in embryo implantation and in the treatment of cancer, arthritis, and arteriosclerosis. Some of the steroids disclosed in Aristoff, et al. are disclosed in U.S. Patent No. 4,771,042 in combination with heparin or a heparin fragment for inhibiting angiogenesis in a warm blooded animal.

Compositions of hydrocortisone, "tetrahydrocortisol-S," and U-72,745G, each in combination with a beta cyclodextrin, have been shown to inhibit corneal neovascularization: Li, et al., *Angiostatic Steroids Potentiated by Sulphated Cyclodextrin Inhibit Corneal Neovascularization*, Investigative Ophthalmology and Visual Science, Vol. 32, No. 11, pp. 2898-2905 (October, 1991). The steroids alone reduce neovascularization somewhat but are not effective alone in effecting regression of neovascularization.

Some of the compounds of the present invention are disclosed in commonly owned patent application WO 93/10141, for controlling neovascularization and ocular hypertension.

Currently, glucocorticoids or surgical removal of tissue growth are used to try and control disease states associated with scar formation and non-cancerous tissue growth. However, neither approach has proved very effective and there is a need for methods to treat persons with such disease states. The use of the compounds of the present invention fill this need.

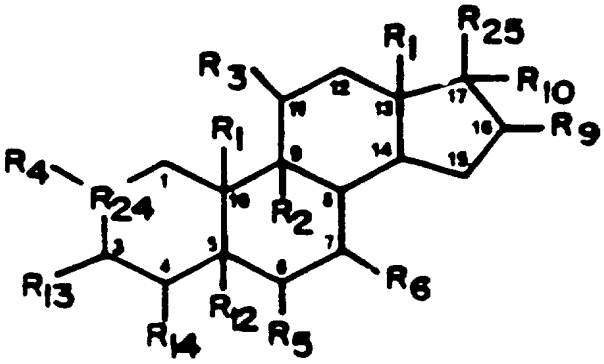
Summary of the Invention

This invention is directed to compounds useful for treating persons with diseases in which non-cancerous tissue growth, including scar formation, plays a pathogenic role. In particular, the compounds are useful for treating pterygium (primary and recurrent), glaucoma filtration bleb failure, hyperkeratosis, cheloid formation, polyp formation and wound healing conditions with excessive scar formation.

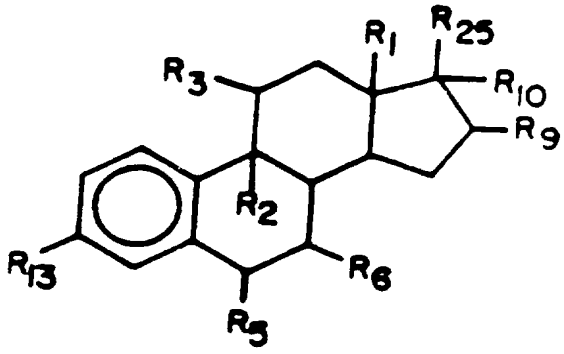
The invention encompasses methods for controlling these diseases through the systemic or local administration of the compositions of the compounds disclosed herein.

Detailed Description of Preferred Embodiments

The compounds of the present invention have the following formula:



Structure [A]



Structure[B]

wherein R_1 is H, β-CH_3 or β-C_2H_5;

R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or -Cl;

R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N$(R)_2$ or -OC(=O)OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from

chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});

R_4 is H, CH_3, Cl or F;

R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;

R_6 is H or CH_3;

R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, $=CH_2$, $CH_2C(=O)OR_{28}$, OR_{26}, $O(C=O)R_{27}$, or $O(C=O)CH_2(C=O)OR_{26}$;

R_{10} is -C≡CH, -CH=CH_2, CH_2OH, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;

R_{12} is H or forms a double bond with R_1 or R_{14};

R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-$P(=O)(OH)_2$, or -O-C(=O)-$(CH_2)_t$COOH where t is an integer from 2 to 6;

R_{14} is H or forms a double bond with R_{12};

R_{15} is H, =O or -OH;

R_{23} is -OH, O-C(=O)-R_{11}, -OP(O)-$(OH)_2$, -O-C(=O)-$(CH_2)_t$COOH or with R_{10} forms a cyclic phosphate wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -Z$(CH_2)_r$Q,

wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,-$CON(R_{18})$-, -$N(R_{18})$CO-, -O-, -S-, -S(O)-, or -$S(O_2)$-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;

Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -$S(O)_2$-, -$SO_2N(R_{20})$-, or $N(R_{20})$ SO_2-; and R_{20} is hydrogen or lower alkyl-(C_1-C_4); with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

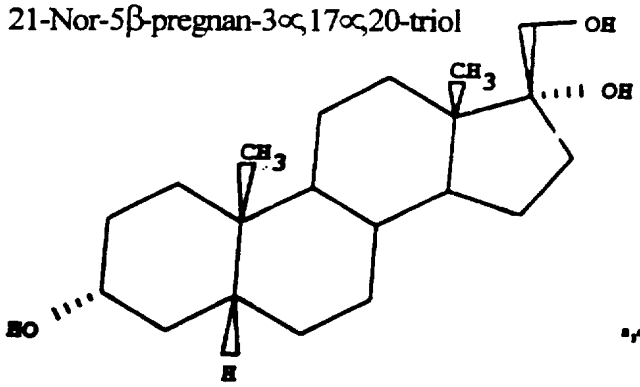
(3) $CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H, CH_3, -CH_2COOH, -

CH_2CH_2COOH, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$, or
$-CH_2Ph-OH$ wherein Ph-OH is p-hydroxyphenyl;
or R_{21} is CH_3 and R_{22} is H;
or R_{21} and R_{22} taken together are $-CH_2CH_2CH_2-$;
or $-N(R_{21})CH(R_{22})COOH$ taken together is $-NHCH_2CONHCH_2COOH$; and
pharmaceutically acceptable salts thereof;
with the proviso that except for the compound wherein R_1 is $-CH_3$, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is α-F, R_9 is β-CH_3, R_{10} is α-OH, R_{13} and R_{15} are =O and R_{23} is $-OP(O)-(OH)_2$, R_{13} is =O only when R_{23} with R_{10} forms the above described cyclic phosphate.
R_{24} = C, C_1-C_2 double bond, O;
R_{25} = $C(R_{15})CH_2-R_{23}$, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}C(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;
wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl); R_{27} = R_{26} + OR_{26}; R_{28} = H, C1-C6 (alkyl, branched alkyl, cycloalkyl).

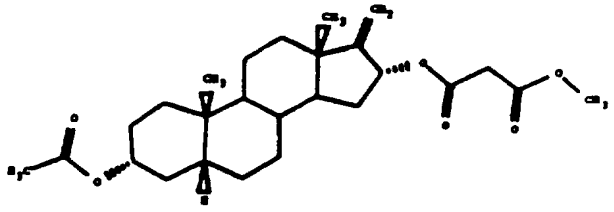
Unless specified otherwise, all substituent groups attached to the cyclopentanophenanthrene moiety of Structures [A] and [B] may be in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts of the compounds.

Preferred compounds are:

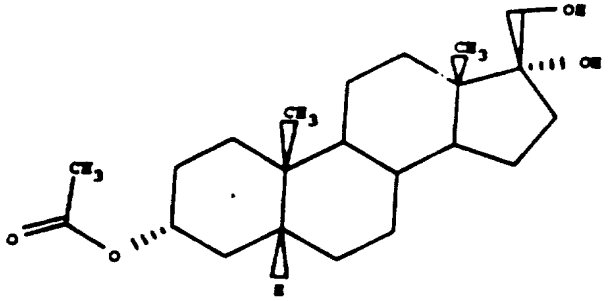
21-Nor-5β-pregnan-3∝,17∝,20-triol



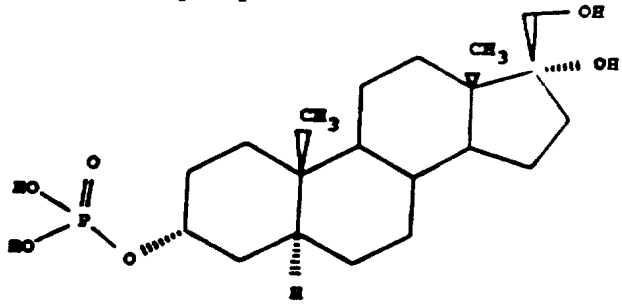
21-Nor-5β-pregn-17(20)en-3∝,16-diol-3-acetate-16-(O-methyl)malonate



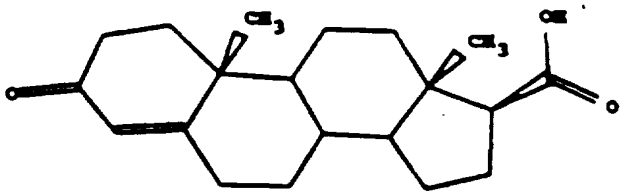
21-Nor-5β-pregnan-3∝,17∝,20-triol-3-acetate



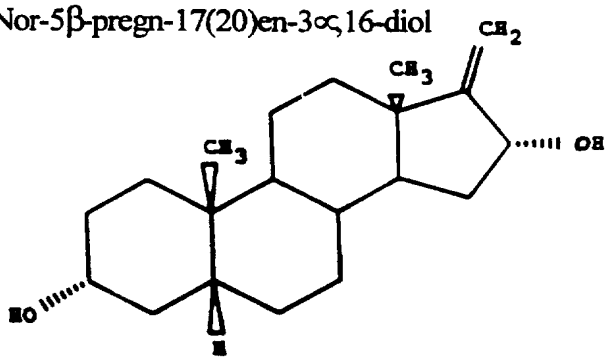
21-Nor-5∝-pregnan-3∝,17∝,20-triol-3-phosphate



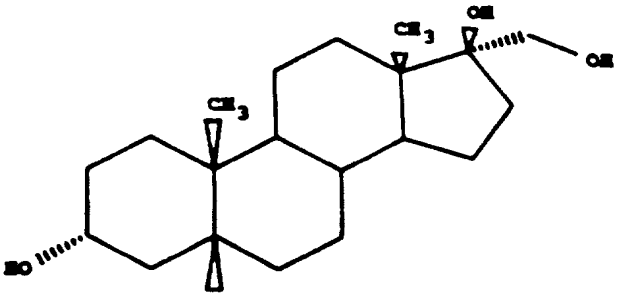
4-Androsten-3-one-17β-carboxylic acid



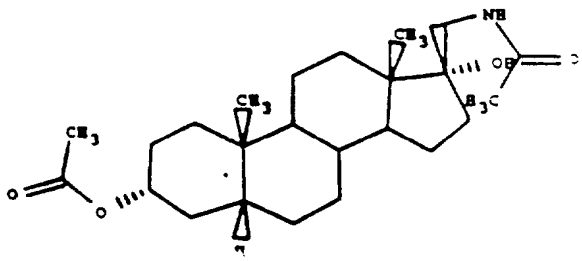
21-Nor-5β-pregn-17(20)en-3∝,16-diol



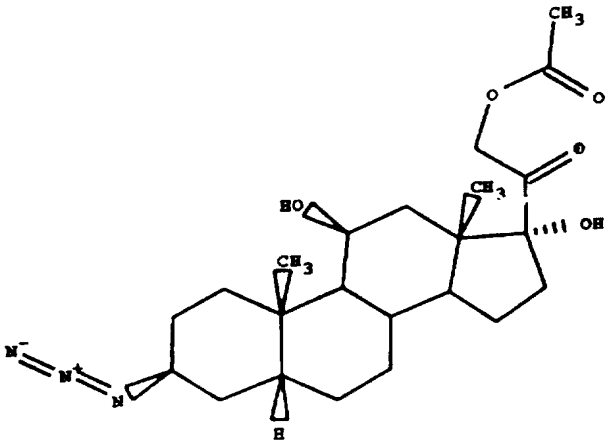
21-Nor-5β-pregnan-3∝,17β,20-triol



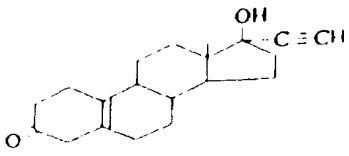
20-Acetamido-21-nor-5β-pregnan-3∝,17∝-diol-3-acetate



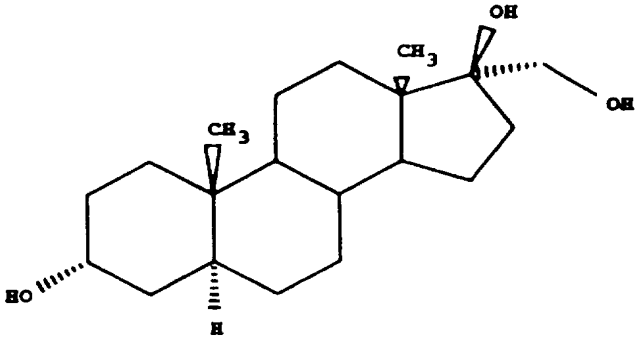
3β-Azido-5β-pregnan-11β,17∝,21-triol-20-one-21-acetate



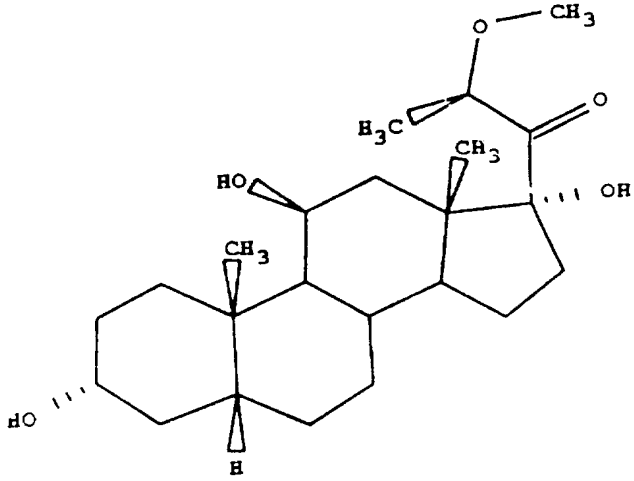
17∝-Ethynyl-5(10)-estren-17β-ol-3-one



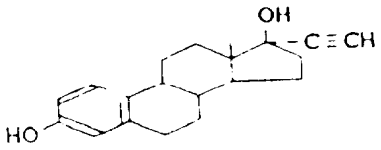
21-Nor-5∝-pregnan-3∝,17β,20-triol



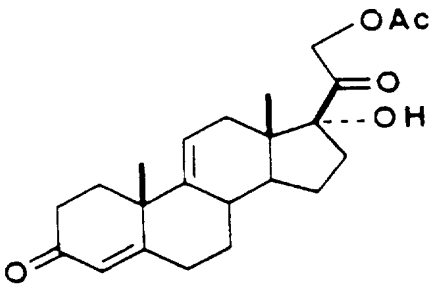
21∝-Methyl-5β-pregnan-3∝,11β,17∝,21-tetrol-20-one-21-methyl ether



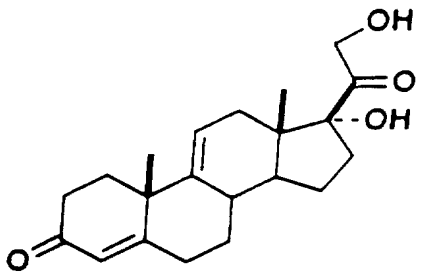
17∝-Ethynyl-1,3,5(10)-estratrien-3,17β-diol



4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate



4,9(11)-Pregnadien-17∝,21-diol-3,20-dione



Most preferred compounds are:

4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate

4,9(11)-Pregnadien-17∝,21-diol-3,20-dione

21-Nor-5β-pregn-17(20)-en-3∝,16-diol-3-acetate-16-(O-methyl)malonate

21-Nor-5β-pregnan-3∝,17∝,20-triol-3-acetate

21-Nor-5∝-pregnan-3∝,17∝,20-triol-3-phosphate

4-Androsten-3-one-17β-carboxylic acid

The compounds of the present invention are useful in preventing and treating persons with diseases in which non-cancerous tissue growth plays a pathogenic role. In particular, the compounds are useful in treating persons suffering from pterygium (primary and recurrent), glaucoma filtration bleb failure, hyperkeratosis, cheloid formation, polyp formation, and post-surgical wound healing conditions with excessive scar formation, such as burns and cuts, including surgical cuts.

The compounds of the present invention may be incorporated in various formulations for delivery. The type of formulation (topical or systemic) will depend on

the site of disease and its severity. For administration to the eye, topical formulations can be used and can include ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride, and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations, a compound is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations comprising the compounds of the present invention can be prepared by suspending a compound in a hydrophilic base prepared from a combination of, for example, Carbachol-974P (a carboxy vinyl polymer available from the BF Goodrich Company) according to published formulations for analogous ophthalmic preparations. Preservatives and antimicrobial agents may also be incorporated in such gel formulations. Systemic formulations can also be used, for example, orally ingested tablets, suppositories, transdermal patches, and formulations for intraocular injection.

The specific type of formulation selected will depend on various factors, such as the compound or its salt being used, the dosage frequency, and the disease being treated. Topical aqueous solutions, suspensions, ointments, creams and gels are the preferred dosage forms for the treatment of pterygium, hyperkeratosis, and cheloid and polyp formation. Topical ophthalmic formulations are suitable for preventing glaucoma filtration bleb failure or scar formation associated with ophthalmic surgery. The compound will normally be contained in these formulations in an amount from about 0.01 to about 10.0 weight/percent. Preferable concentrations range from about 0.1 to about 5.0 weight/percent. Thus, for topical administration, these formulations are delivered to the disease site one to six times a day, depending on the routine discretion of the skilled clinician. Systemic administration, for example, in the form of tablets or suppositories is useful for the treatment of polyp formation. Tablets containing 10-1000 mg of a compound can be taken 2-3 times per day depending on the discretion of the skilled clinician.

The following examples illustrate formulations of the present invention, but are in no way limiting.

Example 1

Topical ocular suspension

Ingredient	Amount (wt.%)
Compound	0.01 - 5.0
Tyloxapol	0.01 to 0.05
HPMC	0.5
Benzalkonium chloride	0.01
Sodium chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

The formulation is prepared by first placing a portion of the purified water into a beaker and heating to 90°C. The hydroxypropylmethylcellulose (HPMC) is then added to the heated water and mixed by means of vigorous vortex stirring until all of the HPMC is dispersed. The resulting mixture is then allowed to cool while undergoing mixing in order to hydrate the HPMC. The resulting solution is then sterilized by means of autoclaving in a vessel having a liquid inlet and a hydrophobic, sterile air vent filter.

The sodium chloride and the edetate disodium are then added to a second portion of the purified water and dissolved. The benzalkonium chloride is then added to the solution, and the pH of the solution is adjusted to 7.4 with 0.1M NaOH/HCl. The solution is then sterilized by means of filtration.

The Compound, 4,9(11)-Pregnadien-17α,21-diol-3,20-dione-21-acetate, is sterilized by either dry heat or ethylene oxide. If ethylene oxide sterilization is selected, aeration for at least 72 hours at 50°C is necessary. The sterilized Compound is weighed aseptically and placed into a pressurized ballmill container. The tyloxapol, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added

to the container and the contents of the container are milled aseptically at 225 rpm for 16 hours, or until all particles are in the range of approximately 5 microns.

Under aseptic conditions, the micronized drug suspension formed by means of the preceding step is then poured into the HPMC solution with mixing. The ballmill container and balls contained therein are then rinsed with a portion of the solution containing the sodium chloride, the edetate disodium and benzalkonium chloride. The rinse is then added aseptically to the HPMC solution. The final volume of the solution is then adjusted with purified water and, if necessary, the pH of the solution is adjusted to pH 7.4 with NaOH/HCl. The formulation will be given topically, in a therapeutically effective amount. In this instance, the phrase "therapeutically effective amount" means an amount which is sufficient to substantially prevent or reverse any ocular neovascularization. The dosage regimen used will depend on the nature of the neovascularization, as well as various other factors such as the patient's age, sex, weight, and medical history.

Example 2

Tablet:

10-1000 mg of a compound of the present invention with inactive ingredients such as starch, lactose and magnesium stearate can be formulated according to procedures known to those skilled in the art of tablet formulation.

Example 3

FORMULATION FOR STERILE INTRAOCULAR INJECTION

each mL contains:	
4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate	10-100 mg
Sodium Chloride	7.14 mg
Potassium Chloride	0.38 mg
Calcium chloride dihydrate	0.154 mg
Magnesium chloride hexahydrate	0.2 mg
Dried sodium phosphate	0.42 mg
Sodium bicarbonate	2.1 mg
Dextrose	0.92 mg
Hydrochloric acid or sodium hydroxide to adjust pH to approximately 7.2	
Water for injection	

Example 4

FORMULATION FOR TOPICAL OCULAR SOLUTION

21-Nor-5∝-pregnan-3∝,17∝-20-triol -3-phosphate	1.0%
Benzalkonium chloride	0.01%
HPMC	0.5%
Sodium chloride	0.8%
Sodium phosphate	0.28%
Edetate disodium	0.01%
NaOH/HCl	q.s. pH 7.2
Purified Water	q.s. 100 mL

Example 5

FORMULATION FOR TOPICAL DERMATOLOGICAL USE

Cream: 4,9(11)-Pregnadien-17α,21-diol-3-20-dione 1 mg/g in cream base of purified water, emulsifying wax, propylene glycol, stearic acid, isopropyl palmitate, synthetic beeswax, polysorbate 60, potassium sorbate, sorbic acid, propyl gallate, citric acid, and sodium hydroxide

Ointment: 1 mg/g of a compound of the present invention in base of mineral oil and polyethylene

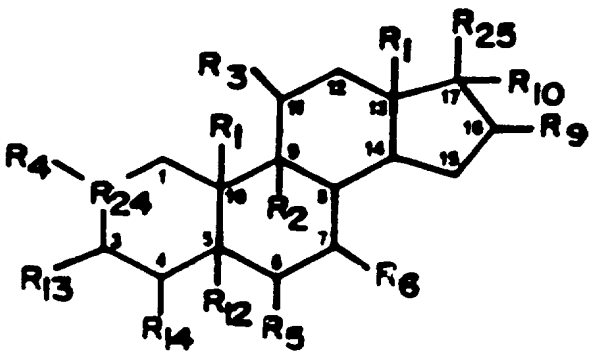
Example 6

FORMULATION FOR SUPPOSITORY

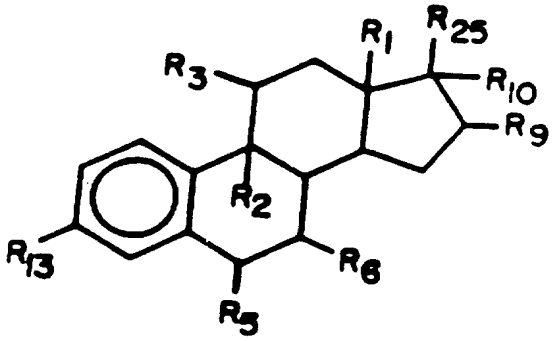
10-500 mg of a compound of the present invention with the following inactive ingredients: glycerin, butylated hydroxytoluene, butylated hydroxyanisole, edetic acid, polyethylene glycol, and sodium chloride

We Claim:

1. A composition for treating diseases in mammals in which non-cancerous tissue growth plays a pathogenic role, comprising a therapeutically effective amount of a compound of the following formula:



Structure [A]



Structure[B]

wherein R_1 is H, β-CH_3 or β-C_2H_5;

R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or -Cl;

R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, $-OC(=O)N(R)_2$ or $-OC(=O)OR_7$, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is $-(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});

R_4 is H, CH_3, Cl or F;

R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;

R_6 is H or CH_3;

R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, $=CH_2$, or $CH_2C(=O)OR_{28}$, OR_{26}, $O(C=O)R_{27}$, or $O(C=O)CH_2(C=O)OR_{26}$;

R_{10} is -C≡CH, $-CH=CH_2$, CH_2OH, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10}

forms a second bond between positions C-16 and C-17;

R_{12} is H or forms a double bond with R_1 or R_{14};

R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-P(=O)$(OH)_2$, or -O-C(=O)-$(CH_2)_t$COOH where t is an integer from 2 to 6;

R_{14} is H or forms a double bond with R_{12};

R_{15} is H, =O or -OH;

R_{23} is -OH, O-C(=O)-R_{11}, -OP(O)-$(OH)_2$, -O-C(=O)-$(CH_2)_t$COOH or with R_{10} forms a cyclic phosphate wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -Z$(CH_2)_r$Q,

wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)-, or -S(O_2)-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;

Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -S$(O)_2$-, -SO_2N(R_{20})-, or N(R_{20}) SO_2-; and R_{20} is hydrogen or lower alkyl-(C_1-C_4); with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

(3) CON(R_{21})CH(R_{22})COOH wherein R_{21} is H and R_{22} is H, CH_3, -CH_2COOH, -CH_2CH_2COOH, -CH_2OH, -CH_2SH, -$CH_2CH_2SCH_3$, or -CH_2Ph-OH wherein Ph-OH is p-hydroxyphenyl;

or R_{21} is CH_3 and R_{22} is H;

or R_{21} and R_{22} taken together are -$CH_2CH_2CH_2$-;

or -N(R_{21})CH(R_{22})COOH taken together is -$NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;

with the proviso that except for the compound wherein R_1 is -CH_3, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is -F, R_9 is -CH_3,

R_{10} is -OH, R_{13} and R_{15} are =O and R_{23} is $-OP(O)-(OH)_2$, R_{13} is =O only when R_{23} with R_{10} forms the above described cyclic phosphate;

R_{24} = C, C_1-C_2 double bond, O;

R_{25} = $C(R_{15})CH_2-R_{23}$, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}C(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;

wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl); R_{27} = R_{26} + OR_{26}; R_{28} = H, C1-C6 (alkyl, branched alkyl, cycloalkyl);

2. The composition of Claim 1 wherein the compound is selected from the group consisting of 21-Nor-5β-pregnan-3∝,17∝,20-triol; 21-Nor-5β-pregn-17(20)en-3∝,16-diol-3-acetate-16-(O-methyl)malonate; 21-Nor-5β-pregnan-3∝,17∝,20-triol-3-acetate; 21-Nor-5∝-pregnan-3∝,17∝,20-triol-3 phosphate; 4-Androsten-3-one-17β-carboxylic acid; 21-Nor-5β-pregn-17(20)en-3∝,16-diol; 21-Nor-5β-pregnan-3∝,17β,20-triol; 20-Acetamido-21-nor-5β-pregnan-3∝,17∝-diol-3-acetate; 3β-Azido-5β-pregnan-11β,17∝,21-triol-20-one-21-acetate; 17∝-Ethynyl-5(10)-estren-17β-ol-3-one; 21-Nor-5∝-pregnan-3∝,17β,20-triol; 21∝-Methyl-5β-pregnan-3∝,11β,17∝, 21-tetrol-20-one-21-methyl ether; 17∝-Ethynyl-1,3,5(10)-estratrien-3,17β-diol; 4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate; and 4,9(11)-Pregnadien-17∝,21-diol-3,20-dione.

3. The composition of Claim 2 wherein the compound is 4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate.

4. The composition of Claim 1 wherein the compound concentration is 0.01 - 10.0 wt.%.

5. The composition of Claim 4 wherein the concentration is 0.1 - 5.0 wt.%.

6. A method for treating diseases in mammals in which non-cancerous tissue growth plays a pathogenic role, which comprises: administering a therapeutically effective amount of the composition of Claim 1.

7. The method of Claim 6 wherein the compound is selected from the group consisting of 21-Nor-5β-pregnan-3∝,17∝,20-triol; 21-Nor-5β-pregn-17(20)en-3∝,16-diol-3-acetate-16-(O-methyl)malonate; 21-Nor-5β-pregnan-3∝,17∝,20-triol-3-acetate; 21-Nor-5∝-pregnan-3∝,17∝,20-triol-3 phosphate; 4-Androsten-3-one-17β-carboxylic acid, 21-Nor-5β-pregn-17(20)en-3∝,16-diol; 21-Nor-5β-pregnan-3∝,17β,20-triol; 20-Acetamido-21-nor-5β-pregnan-3∝,17∝-diol-3-acetate; 3β-Azido-5β-pregnan-11β,17∝,21-triol-20-one-21-acetate; 17∝-Ethynyl-5(10)-estren-17β-ol-3-one; 21-Nor-5∝-pregnan-3∝,17β,20-triol; 21∝-Methyl-5β-pregnan-3∝,11β,17∝, 21-tetrol-20-one-21-methyl ether; 17∝-Ethynyl-1,3,5(10), 4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate; and 4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-estratrien-3,17β-diol.

8. The method of Claim 7 wherein the compound is 4,9(11)-Pregnadien-17∝,21-diol-3,20-dione-21-acetate.

9. The method of Claim 6 wherein the non-cancerous tissue growth is selected from the group consisting of pterygium, glaucoma filtration bleb failure, hyperkeratosis, cheloid formation, polyp formation, and wound healing conditions.

10. The method of Claim 6 wherein the compound concentration is 0.01 - 10 wt.%.

11. The method of Claim 10 wherein the compound concentration is 0.1 to 5.0 wt.%.

12. The method of Claim 6 wherein the composition is administered topically to the disease site.

13. The method of Claim 6 wherein the composition is administered systemically.

INTERNATIONAL SEARCH REPORT

Inten ıal Application No
PCT/US 97/02809

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 10141 A (ALCON) 27 May 1993 cited in the application	1-5
Y	see claims	6-13
Y	US 4 939 135 A (ROBERTSON ET AL.) 3 July 1990 see the whole document	6-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 1997	0 3. 07. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ional application No.
PCT/US 97/02809

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.
SEE ALSO NEXT PAGE

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The subject matter of claims 6-13 can be considered to be insufficiently disclosed given the fact that no data on the pharmacological effects are presented. Moreover the number of different compounds covered by the formulas of claim 1 is too big to make a complete search economically unviable. As no data are presented to make it credible that all or a large number of these compounds share the same activity, the search has been limited to those specific compounds mentioned in the claims and the description.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inten ıal Application No
PCT/US 97/02809

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9310141 A	27-05-93	US 5371078 A	06-12-94
		AU 3223593 A	15-06-93
		CA 2123405 A	27-05-93
		EP 0614463 A	14-09-94
		JP 7501081 T	02-02-95
US 4939135 A	03-07-90	US 5360611 A	01-11-94
		US 5401509 A	28-03-95
		US 5401510 A	28-03-95
		US 5525349 A	11-06-96
		US 5582835 A	10-12-96
		US 5573775 A	12-11-96
		US 5580570 A	03-12-96
		US 5589184 A	31-12-96
		US 5589185 A	31-12-96
		US 5124392 A	23-06-92
		US 5271939 A	21-12-93